

-67-

We claim:

1. A formulation comprising FSH or a FSH
5 variant, containing an alpha and beta subunit, and a
preservative selected from the group consisting of phenol,
m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol,
alkylparaben (methyl, ethyl, propyl, butyl and the like),
10 benzalkonium chloride, benzethonium chloride, sodium
dehydroacetate and thimerosal, or mixtures thereof in an
aqueous diluent.
2. A formulation of Claim 1, wherein the
preservative is phenol, m-cresol, chlorocresol, or a mixture
thereof.
- 15 3. A formulation of Claim 2, wherein the
concentration of FSH or a FSH variant is about 1.0 µg/ml to
about 50 mg/ml.
4. A formulation of Claim 3, further comprising
an isotonicity agent.
- 20 5. A formulation of Claim 4, further comprising
a physiologically acceptable buffer.
6. A formulation comprising FSH or a FSH variant
lyophilized in a first vial, and a second vial containing a
preservative selected from the group consisting of phenol,
25 m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol,
alkylparaben (methyl, ethyl, propyl, butyl and the like),
benzalkonium chloride, benzethonium chloride, sodium
dehydroacetate and thimerosal, or mixtures thereof in an
aqueous diluent.
- 30 7. A formulation of Claim 1, wherein said FSH or
a FSH variant and preservative are in solution.
8. A formulation of Claim 1, wherein said FSH or
a FSH variant is at least one compound selected from the
group consisting of:
- 35 (a): α-subunit: (SEQ ID NO:1)

0922198 081001

-68-

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:2)

5 RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α -subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPIYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β -subunit: (SEQ ID NO:4)

10 NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

(c): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

15 β -subunit: (SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d): α -subunit: (SEQ ID NO:7)

20 FPDGEFTMQGCPECKLKENKYFSKLGAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:8)

NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit: (SEQ ID NO:9)

25 FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:10)

RSCELTNITITVEKEECDFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSDIRE

30 (f): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:11)

35 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

"00180" 86182660

-69-

(g): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

 β -subunit: (SEQ ID NO:12)

5 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

10 β -subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

15 9. A method of treating infertility which
comprises administering to a patient in need thereof a
formulation according to Claim 1.

10. A method of Claim 9, wherein said
patient is selected from the group consisting of a human,
sheep, cow, pig, horse, or rabbit.

20 11. A process for preparing a preserved
solution formulation of FSH or a FSH variant, containing an
alpha and beta subunit, which comprises admixing said FSH or
a FSH variant and a preservative selected from the group
consisting of phenol, m-cresol, p-cresol, o-cresol,
25 chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl,
propyl, butyl and the like), benzalkonium chloride,
benzethonium chloride, sodium dehydroacetate and thimerosal,
or mixtures thereof, in an aqueous diluent.

30 12. An article of manufacture for human
pharmaceutical use, comprising packaging material and a vial
comprising a solution of FSH or a FSH variant, containing an
alpha and beta subunit, and a preservative solution, wherein
said packaging material comprises a label which indicates
that said solution may be held over a period of 24 hours or
35 greater.

0928193 081001

-70-

13. The article of manufacture of Claim 12, wherein said vial is a glass container having a stopper for multi-use administration.

14. The article of manufacture of Claim 12, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

15. The article of manufacture of Claim 12, wherein said vial is a pen-injector device.

16. An article of manufacture, comprising packaging material, a first vial comprising lyophilized FSH or a FSH variant, containing an alpha and beta subunit, and a second vial comprising a preservative solution, wherein said packaging material comprises a label which instructs a patient to reconstitute the said lyophilized FSH or a FSH variant in the preservative solution for use over a period of of 24 hours or greater.

17. The article of manufacture of Claim 16, wherein said first vial and said second vial are embodied in a pen-injector device.

18. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, in an preserved solution, said solution being suitable for administration over a period of 24 hours or greater.

19. A method of using a stable solution of FSH or a FSH variant, containing an alpha and beta subunit to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of FSH or a FSH variant in a stable solution, said solution being suitable for administration over a period of 24 hours or greater.

20. The use of at least one alpha or beta polypeptide of a FSH or a FSH variant in the preparation of a preserved formulation adapted for administration over a period of 24 hours or greater.

00028198-081001

(c): α -subunit:(SEQ ID NO:5)

~~β-subunit~~: (SEQ ID NO:6)

5

FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTM LVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

10

(e) : α -subunit: (SEQ ID NO: 9)

15

RSCELTNITITVEKEECSCFISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKE
LVYETVKVPGCAHHADSLYTYPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIR
E

20

β -subunit: (SEQ ID NO:11)

25

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHHKS

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHHKS

β -subunit: (SEQ ID NO:13)

-73-

NSCELTNITIAIEKEEFCRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

28. A method of treating infertility which
5 comprises administering to a patient in need thereof a
formulation according to Claim 21.

29. A method of Claim 28, wherein said
patient is selected from the group consisting of a human,
sheep, cow, pig, horse, or rabbit.

10 30. A process for preparing a stable solution
formulation of FSH or a FSH variant, containing an alpha and
beta subunit, which comprises admixing a FSH or a FSH
variant in phosphate buffer containing saline or a salt.

15 31. An article of manufacture for pharmaceutical
use, comprising packaging material and a vial comprising a
stable solution of FSH or a FSH variant, containing an alpha
and beta subunit, in an aqueous diluent, wherein said
packaging material comprises a label which indicates that
20 such solution is suitable for use over a period of 24 hours
or greater.

32. The article of manufacture of Claim 31,
wherein said vial is a glass container having a stopper for
multi-use administration.

25 33. The article of manufacture of Claim 31,
wherein said vial is a blister pack, capable of being
punctured and used in pulmonary administration.

34. The article of manufacture of Claim 31,
wherein said vial is a pen-injector device.

30 35. An article of manufacture, comprising
packaging material, a first vial comprising a lyophilized
FSH or a FSH variant containing, an alpha and beta subunit,
and a second vial comprising a stable aqueous diluent,
wherein said packaging material comprises a label which
instructs a patient to reconstitute said FSH or a FSH
35 variant in the aqueous diluent to form a solution that is
suitable for use over a period of 24 hours or greater.

0928198 081001

-74-

36. The article of manufacture of Claim 35, wherein said first vial and said second vial are embodied in a pen-injector device.

5 37. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous phosphate buffered diluent, said solution being suitable for administration over a period of 24 hours or greater.

10 38. A method of using a solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant in an aqueous diluent suitable for use over a period
15 of 24 hours or greater.

39. The use of at least one polypeptide of a FSH or a FSH variant in the preparation of a stable formulation adapted for administration over a period of 24 hours or greater.

20 40. A formulation as described herein.

41. An article of manufacture as described herein

42. A process as described herein.

43. A use as described herein.

44. A method as described herein.

25 45. Use of a formulation of claim 1 for treating infertility in a patient in need thereof

46. Use of a formulation of claim 1 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

30 47. Use of a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, said solution being suitable for administration over a period of 24 hours or greater.

35 48. Use of a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat

0928198 081001

5 49. Use of a formulation of Claim 21 for treating
infertility in a patient in need thereof.

10 51. Use of stable stable solution of purified FSH
or a FSH variant, containing an alpha and beta subunit, in a
phosphate buffer containing saline or a salt suitable for
administration over a period of 24 hours or greater for
treating infertility in a patient in need thereof.

53. A process of producing a formulation comprising admixing FSH or a FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

30 54. A process of producing a stable formulation comprising admixing at least one FSH or a FSH variant, containing an alpha and beta subunit, and a phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

-76-

55. A process of Claim 53, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

56. A process according to any of Claims 53-54, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

57. A process according to any of Claims 53-54, further admixing an isotonicity agent.

58. A process of Claim 53-54, further admixing a physiologically acceptable buffer.

59. A process comprising preparing a FSH or a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

60. A process of Claim 59, wherein said FSH or a FSH variant and preservative are further put into solution.

61. A process according to any of claims 53-54, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit:(SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTM LVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit:(SEQ ID NO:2)

RSELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α-subunit:(SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPPIYQCKGCCFSRAYPTPARSRKTM LVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit:(SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNSDSTDCTVRGLGPSYCSFGDMKE

T00180" 86T32660

5

β -subunit: (SEQ ID NO:6)

10

β -subunit:\(SEQ ID NO:8)

15

β-subunit: (SEQ ID NO:10)

20

β-subunit: (SEQ ID NO: 11)

25

β-subunit: (SEQ ID NO:12)

30

β-subunit: (SEQ ID NO:13)

WO 00/04913

PCT/US99/16031

- 78 -

NSCELTNITIAIEKEECRPOISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

add B17

add
B1

FOOT 80" 86T82660